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JANE MASSEY LICATA, ESQ.
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ  08053

| EXAMINER |
|---|
| FREDMAN, JEFFREY NORMAN |

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## BEFORE THE BOARD OF PATENT APPEALS
## AND INTERFERENCES

Paper No. 20031029

Application Number: 09/181,601
Filing Date: October 29, 1998
Appellant(s): ANDERSON ET AL.

Jane Massey Licata
For Appellant

## EXAMINER'S ANSWER

This is in response to the appeal brief filed September 16, 2003.

## *(1)    Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

## *(2)    Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly

affect or be directly affected by or have a bearing on the decision in the pending appeal

is contained in the brief.

## *(3)    Status of Claims*

The statement of the status of the claims contained in the brief is correct.

## *(4)    Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection

contained in the brief is correct.

## *(5)    Summary of Invention*

The summary of invention contained in the brief is correct.

## *(6)    Issues*

The appellant's statement of the issues in the brief is substantially correct. The

changes are as follows:

Appellant argues that issues 2) , 3) and 4) rely on Wallace in view of Holm

without reliance on Farber. However, in view of Appellant's after final amendment filed

February 18, 2003, which amended the step of parsing from claim 2 into the

independent claim, the remaining rejections now include Farber, as applied to the

cancelled claim 2. As per MPEP 1208, the alteration of the rejection to address the

claims as amended is not a new grounds of rejection.

### (7)    *Grouping of Claims*

The rejection of claims 1, 3-6 and 11-14 stand or fall together because

appellant's brief includes a statement that this grouping of claims stands or falls

together.  See 37 CFR 1.192(c)(7).

### (8)    *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

### (9)    *Prior Art of Record*

Wallace et al, "Derivation of 3D coordinate templates for searching structural

databases: Application to Ser-His-Asp catalytic triads in the serine proteases and

lipases", Protein Science, vol 5, (June 1996), pp. 1001-1013.

Farber et al, "Determination of Eukaryotic Protein Coding Regions Using Neural

Networks and Information Theory" J. Mol. Biol. vol. 226 (1992), pp. 471-479.

Friedrichs et al, "An automated procedure for the assignment of protein $^1HN$, $^{15}N$, $^{15}Ca$,

$^1H^{\alpha}$, $^{13}C^{\beta}$, and $^1H^{\beta}$, resonances", J. Biomolecular NMR, vol. 4 (1990), pp. 703-726.

Holm et al, "DALI : A network tool f or protein structure comparison" , Trends

Biotechnol. vol. 85 (1995) pp. 478-480.

Bagby et al, "The button test: A small scale method using microdialysis cells for

assessing protein solubility at concentrations suitable for NMR" J. Biomolecular NMR,

vol. 10 (1997), pp. 279-282.

## *(10)    Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

### *Claim Rejections - 35 USC § 103*
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for

all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors.  In considering patentability of

the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary.  Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g)

prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6 and 11-14  are rejected under 35 U.S.C. 103(a) as being

unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm

et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992)

226:471-479).

Wallace teaches a method for determining a biochemical function of a protein or

polypeptide domain of unknown function (abstract) comprising: a) identifying a putative

polypeptide domain that properly folds into a stable polypeptide domain having a

definite three dimensional structure, b) determining the three dimensional structure of

the stable polypeptide domain (page 1004-5, subheading "derivation of 3D templates"),

c) comparing the determined three dimensional structure to known three dimensional

structures in the protein data bank, wherein said comparison identified known

homologous three dimensional structures (page 1009, subheading "search for Ser-His-

Asp triads in other PDB entries"), d) correlating a biochemical function corresponding to

the identified homologous structure to a biochemical function for the stable polypeptide

domain (page 1009, figure 5 and page 1011, columns 1 and 2).

The claim does not require that the determination of three dimensional structure

occur by a physical step, but broadly includes determinations which simply occur inside

the computer algorithm, such as those taught by Wallace.

Wallace teaches identification of domains, but arguably does not teach the use of

domains of 50 to 300 amino acids in length for comparison purposes.

Holm teaches determination of three dimensional structures by cyrstallography or

NMR (page 478, column 3) followed by database analysis using the complete three

dimensional structure of the protein including every amino acid by DALI (page 478,

column 3 and page 479). Holm exemplifies a comparison between urease and

adenosine deaminase (figure 1) in which the complete three dimensional structrures of

the 352 amino acid adenosine deaminase protein is compred to the larger urease

protein. Holm further shows a comparison which was performed for the Adenovirus

type 5 knob domain (see page 478, table 1) which knob domain represents amino acids

386 to 581 of the Adenovirus fiber protein, resulting in a comparison of 195 amino acids, within the claim domain size range.

.       It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace with the NMR and Crystallization techniques, taught by Holm and well known in the art for structure determination purposes and with the use of domains within the range of 50-300 amino acids since Holm teaches screening domains of those sizes.  An ordinary practitioner would have been motivated to utilize database analysis of Holm in the method of Wallace since Wallace states "As the number of known protein structures increases, so the need for a 3D equivalent of PROSITE grows with it, especially for likely functions of proteins whose biological role is unknown (page 1001, column 1)".  Thus, Wallace expressly notes that there is a need for methods of 3D comparison of proteins in order to determine the biochemical function of unknown proteins.  Holm satisfies and answers this need to determine the relatioship of unknown to known proteins.  Holm states "At the last stages of solving a new protein structure, crystallographers and nuclear magnetic resonance (NMR) spectroscopists are keen to know if their structure represents a unique protein fold or if it has an unexpected structural similiarity to a known protein fold.  To answer these questions, the DALI server performs a database search with a new structure against all structures in the Protein Data Bank. (Page 478, column 3)".   Thus, Holm expressly notes that the ordinary practitioner in this art is motivated to perform a comparison to determine the relationship of the new protein with proteins present in the database, thereby fulfilling the stated need and motivation of Wallace.

Wallace in view of Friedrichs does not teach a prestep of parsing a database to identify the protein coding regions.

Farber teaches a method of discriminating open reading frames (abstract and pages 472-474).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace in view of Holm with the database preparation method of Farber since Farber notes "Simple neural networks predict coding regions in DNA very well when trained on a representation of DNA using single codon frequencies (page 478, column 1)". An ordinary practitioner would have been motivated to combine the method of Wallace in view of Holm with the protein coding determinations of Farber in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

Claims 1, 5-9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726).

Wallace in view of Holm and further in view of Farber et al teach the limitations of claims 1, 5, 6 and 11-14 as discussed above. Wallace in view of Holm and further in view of Farber et al determines the three dimensional structure of the stable domain by reference to the protein database and suggests the use of NMR. However, Wallace in view of Holm and further in view of Farber et al does not teach the specific NMR characterization techniques nor automated NMR assignments.

Friedrichs teaches determination of the correctness of a protein structure using a variety of NMR spectrometer spectra (page 705) and automated analysis of these spectra using a computer program (pages 708-715). Friedrichs further teaches amide hydrogen exchanges (pages 705 and 708).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace with the use of NMR structural determination of Friedrichs since Wallace states "This suggests that the development of databases of 3D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions (abstract)". Here, Wallace expressly motivates the determination of new protein structures. Motivation to use NMR in this determination is provided by Friedrich, who states "The choice of NMR experiments was based on considerations regarding the sensitivity and resolution of spectra for medium to large-sized proteins (page 720)". Friedrich further motivates the automated assignment of NMR spectra in this determination, noting "Instead of taking weeks, the backbone assignments can be made in one or two days following data acquisition and processing (page 722)". An ordinary practitioner would have been motivated to utilize NMR to determine protein structures in order to sensitively and accurately provide data for 3D determinations and would have been motivated to utilize the automated assignments of Friedrichs in order to minimize the time needed to determine the 3D structure as expressly motivated by Friedrichs.

Claims 1, 5-9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726) and further in view of Bagby et al (J. Biomol. NMR (1997) 10:279-282).

Wallace in view of Holm and further in view of Farber and further in view of Friedrichs teach the limitations of claims 1, 5-9 and 11-14 as discussed above. Wallace in view of Holm and further in view of Farber and further in view of Friedrichs do not teach the button test for microdialysis and NMR.

Bagby teaches a method for preparing samples for NMR to determine optimal solubilization comprising the steps: a) preparing an array of microdialysis buttons with 5 ul containing at least 1 mM protein (page 280), b) dialyzing each member of the array against a different buffer (page 280), c) analyzing the sample to determine if the protein remained soluble (page 280) and d) selecting the optimum solubility for NMR (page 280). Bagby expressly notes a lab expressed the desired protein (page 281, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the button test of Bagby with the NMR and functional determination method of Wallace in view of Holm and further in view of Friedrichs since Bagby states "The button test is an efficient, small scale way of tackling this problem.(page 281, column 1)". An ordinary practitioner would have been motivated to utilize the button test to optimize solubility for NMR since it is expressly noted as efficient and small scale, which reduced time and wasted reagents, which for purified proteins can represent a large investment of time and money.

Claims 1-9, 11-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479) ) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726).

Wallace in view of Holm and further in view of Friedrichs and further in view of Farber teach the method of the claims as discussed above. Wallace in view of Friedrichs and further in view of Farber does not teach the use of an integrated system.

It would have been prima facie obvious to one of ordinary skill in the art at the

time the invention was made to use an integrated system because an ordinary

practitioner would have been motivated to combine the reagents, software and

apparatus used in the methods of Wallace in view of Holm and further in view of

Friedrichs and further in view of Farber into an integrated system for determination of

protein function from protein structure in order to simplify the determination of protein

function by collecting reagents of use in an obvious method into a single location to

improve ease of use and minimize effort.

## (11)   Response to Argument

The claimed invention is drawn to a series of steps routinely performed in

biotechnology.  The sequence of protein discovery in the post genomic age is to

sequence a nucleic acid, to identify the protein coding region and then to analyze the

domain to determine the three dimensional structure in order to identify the protein

function.  This routine process is well laid out in the Wallace Abstract, which states

(emphasis added):

> "**It is well established that sequence templates (e.g., PROSITE) and
> databases are powerful tools for identifying biological function and tertiary
> structure for an unknown protein sequence**. Here we describe a method for
> automatically deriving 3D templates from the protein structures deposited in the
> Brookhaven Protein Data Bank. As an example, we describe a template derived
> for the Ser-His-Asp catalytic triad found in the serine proteases and
> triacylglycerol lipases. We find that the resultant template provides a highly
> selective tool for automatically differentiating between catalytic and noncatalytic
> Ser-His-Asp associations. When applied to nonproteolytic proteins, the template
> picks out two "non-esterase" catalytic triads that may be of biological relevant.
> This suggests that the development of databases of 3D templates, such as those
> that currently exist for protein sequence templates, will help **identify th⁻
> functions of new protein structures** as they are determined and pinpoint their
> functionally important regions"

So Wallace expressly teaches the well established, routine, and entirely ordinary idea that new sequences are searched for sequence patterns towards the goal of determining the function of the protein. These claims simply write these routine elements, ordinarily performed by the routine scientist, but ordinarily separated by routineer into the least publishable unit. Further, many of these steps, particularly the step of parsing the unknown nucleic acid into its open reading frames, are so routine, that they are not listed in scientific publications, which is the reason that the Farber reference was required for the original claim 2.

Appellant initially argues that the rejection, and Wallace in particular, does not teach the use of a domain of 50 to 300 amino acids. This argument is not correct on several levels. First, Wallace teaches formation of 3D templates based upon secondary structure, stating on page 1004 that "The second of our two data sets was a representative set of protein structures in the PDB. The 3D templates derived from the enzyme data set were applied to this second data set to see if any Ser-His-Asp triplets, in the catalytic conformation, are present in any other proteins. The second data set was a set of unique protein chains, including homologues, but excluding identical or trivially different chains such as single-residue mutants. It was compiled by extracting protein chains from the PDB such that no two had a sequence identity greater than 95%. The resultant 639 protein chains are listed in Table 2." The proteins listed in Table 2 are all part of the Wallace data set and were all analyzed using the Wallace method. All of these proteins are larger than 50 amino acids. The argument by Appellant that the "triad" consists of only three amino acids ignores both what Wallace

actually did and what a protein structure comprises. Wallace analyzed the full protein

structures of these proteins to determine the three amino acids involved in the actual

catalysis. A protein structure such as the catalytic triad of Wallace does not represent

three amino acids lost in space, but represents three amino acids, embedded in a

context. That context is provided by all of the other amino acids in the protein chain.

What Wallace did was to analyze the three amino acids in the context of the folds and

three dimensional structure and context provided by all of the remaining amino acids in

the protein. Without that context, and those other amino acids, the method of Wallace

would be nonsensical.

Second, the three amino acids Ser, His and Asp occur in nearly every protein of

appreciable length, but only form the catalytic triad necessary for the protease function

when the remaining amino acids of the protein place these three amino acids in the

proper positions, the proper context, to result in protease function. So when Wallace

performs the analysis, Wallace is expressly using the entire protein sequence imposed

by the each of the amino acids in relationship to one another to determine the catalytic

triad. Wallace expressly teaches that in the quote above, where the data sets were

chosen from the PDB. Wallace does teach that only a part of the data set comprising

less than the entire protein was used. At page 1004, Wallace teaches the use of the

entire data set representing the entire protein sequence.

Therefore, contrary to Appellant's argument, Wallace does not teach away from

the use of 50 to 300 amino acid domains but rather expressly teaches the use of large

amino acid domains such as those found in the serine proteases. Appellant

mischaracterizes the Wallace teaching at page 1002, by arguing that the use of the Ser-
His-Asp catalytic triad was limited to the use of those three amino acids without the
context. As indicated above, such an analysis would yield nonsense. The 3D template
must incorporate the structural elements imposed by the rest of the protein or the
template will not yield any meaningful results. This context provides the remaining
amino acids. This context can be seen throughout the Wallace paper and especially in
figure 7, where the entire structure of the proteins is diagrammatically shown, with
standard secondary structural elements substituting for some of the amino acids such
as beta sheets and alpha helical barrels.

Appellant then argues that the Holm reference does not teach a comparison of
the proper length. As the rejection notes, Holm shows a comparison which was
performed for the Adenovirus type 5 knob domain (see page 478, table 1) which knob
domain represents amino acids 386 to 581 of the Adenovirus fiber protein, resulting in a
comparison of 196 amino acids, within the claim domain size range. It is unclear if
Appellant is traversing whether a comparison was made with the knob region, or the
fact that the knob region is 196 amino acids. Table 1 clearly shows that the knob region
of Adenovirus fiber was analyzed. With regard to the size of the Knob region, Table 1
provides the protein data base code for that protein, which is 1knb. This is simply a
factual matter and if the Protein Data base web site is accessed at
http://www.rcsb.org/pdb/cgi/explore.cgi?job=chains&pdbId=1KNB&page=0&pid=192371
067520961, it is clearly shown that 1knb (which is the database designation for the
adenovirus fiber protein knob) has 196 residues.

Appellant then discusses each of the references and states that each is

incomplete and would not anticipate the claims. In this, Appellant is correct, since none

of the references were cited under 35 U.S.C. 102. In fact, as can be seen in the

rejection above, all of the claims are rejected under 35 U.S.C. 103(a), the obviousness

statute. It is the combination of references, in concert with the motivation provided in

the references and the knowledge supplied in these references, which renders the

claims prima facie obvious. Appellant then launches into a discussion of the three basic

criteria of obviousness.

Appellant first argues that the cited art fails to teach limitations of the claims,

specifically the domain size and the concept of parsing nucleic acids into functional

domains. As noted above, the first issue, domain size, is expressly taught by both

Wallace and Holm. With regard to the concept of parsing nucleic acids, Farber notes

"Simple neural networks predict coding regions in DNA very well when trained on a

representation of DNA using single codon frequencies (page 478, column 1)". Farber

expressly teaches methods to parse nucleic acids into the functional coding regions with

a very high degree of accuracy. Therefore, when Appellant argues that teachings are

missing from the rejections, this statement is not correct. Every element is taught by the

cited prior art.

Appellant then argues the issue of motivation. While specific motivation is cited

in the rejection, whose entire contents are provided above, Appellant raises two points.

First, is Farber in an area distinct from that of Wallace and Holm. This argument is

simply incorrect and untrue. It is standard and beyond standard for any molecular

biologist to utilize computers in the analysis of DNA sequences that encode proteins.

That this is a recognized step in analysis of nucleic acids is shown by Farber, who

states at page 478, column 2 "Achievement of sufficiently high accuracies on short

fragment lengths is critical for a computational means of finding coding regions in

unannotated DNA sequences such as those arising from the mega-base sequencing

efforts of the Human Genome Project." This expressly shows that the determination of

the protein coding regions is linked to the sequencing and protein analysis efforts of the

Human Genome Project.

Second, is there motivation to combine the references. Farber teaches that the

ordinary biochemist, after performing mega base sequencing, would wish to find coding

regions by computational means. An ordinary practitioner would therefore be motivated

to apply the method of Farber to identify the proteins present in the sequenced human

genome. Once that practitioner determined the protein sequence, Wallace teaches that

the ordinary practitioner would wish to identify the function of unknown coding regions,

"will help identify the functions of new protein structures as they are determined and

pinpoint their functionally important regions (abstract)". So there is significant

motivation to integrate these methods in order to take an unknown nucleic acid

sequence and yield the result desired by Wallace, of identifying the function of the

protein structure.

Appellant concludes by arguing that there is no reasonable expectation of

success. The legal standard for "reasonable expectation of success" is provided by

caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not

require absolute predictability, only a reasonable expectation of success; i.e. , a

reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853

F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is

express teaching of Wallace and Holm of how to perform the functional analysis of

proteins by comparing the 3D structures.   Wallace shows successful performance of

the method.   There is further evidence as shown by Farber that 99.4% (see page 478)

of the coding sequences will be correctly parsed by his method.   This sufficient for a

reasonable expectation of success.   The MPEP cites In re O'Farrell, which notes

regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been
> to vary all parameters or try each of numerous possible choices until one
> possibly arrived at a successful result, where the prior art gave either no
> indication of which parameters were critical or no direction as to which of
> many possible choices is likely to be successful. E.g ., In re Geiger , 815
> F.2d at 688, 2 USPQ2d at 1278;  Novo Industri A/S v. Travenol
> Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir.
> 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA
> 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9.  In others, what
> was "obvious to try" was to explore a new technology or general approach
> that seemed to be a promising field of experimentation, where the prior art
> gave only general guidance as to the particular form of the claimed
> invention or how to achieve it.  In re Dow Chemical Co ., 837 F.2d, 469,
> 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985);  Hybritech, Inc. v.
> Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91
> (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987);  In re Tomlinson ;
> 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art of Wallace and Farber teach specific methods which specifically function and are shown to yield working results. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing in how to parse and analyze proteins.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Jeffrey Predman
Primary Examiner
Art Unit 1634

October 30, 2003

Conferees

Gary Benzion, Ph.D.  SPE 1637

Irem Yucel, Ph.D. SPE 1636

JANE MASSEY LICATA, ESQ.
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
Conferee

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
Conferee